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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WORTMAN, DONNA C

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/12/2003

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/515,276	MONTMINY, MARC R.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/27/02, 1/23/03, 3/26/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,12, and 17-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,12 and 17-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on November 27, 2002, has been entered.

Claims 5 and 7 were amended and new claims 18-24 were added in Paper No. 19 filed January 23, 2003. Claims 1, 7, 12, 17, 18, and 24 were amended and claims 25-33 were added in Paper No. 21 filed March 26, 2003. Claims 1-7, 12, and 17-33 are pending and under examination.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description rejection

Claims 1-7, 12, and 17-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of treating an individual suffering from diabetes mellitus, or a method of modulating glucose metabolism in an individual who

has diabetes mellitus, or a method of inhibiting expression of phosphoenolpyruvate carboxykinase (PEPCK) in an individual who has diabetes mellitus, by administering a compound that inhibits binding of cyclic AMP response element binding protein, CREB, to CREB binding protein, CBP, or disrupts a complex comprising CREB and CBP; the inhibiting or disrupting compound is identified by Applicant's patented method (US Patent No. 6,063,583).

The written description requirement is separate and distinct from the enablement requirement. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

The specification of the instant application mentions diabetes treatment in six places:

(1) In the last sentence of the Abstract: "In still another aspect, methods employing compounds which inhibit intracellular signal-induced response pathways have been developed for the treatment of diabetes mellitus."

(2) At page 1, lines 24-26: "In yet another aspect, the present invention relates to methods for treating diabetes mellitus."

(3) At page 3, line 28-page 4, line 8: "The ability to repress intracellular signal-induced response pathways is an important mechanism in negative control of gene expression. Selective disruption of such pathways would allow the development of therapeutic agents capable of treating a variety of disease states related to improper activation and/or expression of specific transcription factors. For example, in patients

with non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia develops, in part as a result of ß cell failure secondary to chronic insulin resistance. This hyperglycemia appears to be exacerbated by hyperglucagonemia and increased hepatic gluconeogenesis. cAMP appears to be the major starvation state signal which triggers glucagon gene expression as well as transcription of PEPCK, the rate limiting enzyme in gluconeogenesis."

(4). At page 4, line 29-page 5, line 2: "In still another aspect, an assay is provided to identify compounds which have the binding and/or activation properties characteristic of CREB binding protein. In still another aspect, methods employing compounds which inhibit intracellular signal-induced response pathways have been developed for the treatment of diabetes mellitus."

(5) At page 20, lines 1-11: "In accordance with a still further embodiment of the present invention, there are provided methods for treating diabetes mellitus, said method comprising contacting a biological system with an amount of an effective amount of a compound which inhibits binding of CREB to CBP. Such methods ameliorate hyperglycemia associated with diabetes mellitus by modulating gluconeogenesis and/or hyperglucagonemia. Particularly, such methods employ compounds which disrupt the formation of CREB:CBP complexes, thus inhibiting transcription of PEPCK or glucagon gene."

(6) In original claims 1-7.

The specification provides Examples I-V, all of which are *in vitro* studies that concern the properties of CBP and the nature of its interactions with other proteins.

It is apparent that the specification conveys the intention to claim diabetes treatment as a part of the invention; however, the specification does not describe a diabetes treatment in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of a diabetes treatment in the form of a compound identified by the disclosed method. Possession may be shown in a variety of ways, including description of an actual reduction to practice; the disclosure of drawings or structural chemical formulas that show that the invention was complete; or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. Reduction to practice may be shown, e.g., by actual testing of the claimed material; in the instant case, the specification does not show a reduction to practice of a diabetes treatment method as claimed. The specification does not describe or disclose the structure of even one compound that has been identified by Applicant's method and treats diabetes. Further, the only identifying characteristic of such compound provided is a functional one, that it disrupt or inhibit binding of CREB to CBP in such a way that it can be identified by Applicant's method. No structural features are given for any identified compound used to treat diabetes. The compound to be used to treat diabetes is therefore described solely in terms of a method of its identification coupled with its function and there is no described or art-recognized correlation or relationship between structure and function of any compound identified by Applicant's method. The description provided in Applicant's specification does not reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Enablement rejection

Claims 1-7, 12, and 17-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining enablement include the breadth of the claims, the nature of the invention, the state of the prior art; the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples; and the quantity of experimentation needed to make or use the invention.

The claims are drawn to a method of treating an individual suffering from diabetes mellitus, or a method of modulating glucose metabolism in an individual, or a method of inhibiting expression of phosphoenolpyruvate carboxykinase (PEPCK) in an individual, by administering a compound that inhibits binding of cyclic AMP response element binding protein, CREB, to CREB binding protein, CBP, or disrupts a complex comprising CREB and CBP; the inhibiting or disrupting compound is identified by Applicant's patented method (US Patent No. 6,063,583).

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The application being appealed is a divisional of application 08/961739, filed October 31, 1997, now US Patent No. 6,063,583, which is a continuation-in-part of 08/194468, now US Patent 5,750,336, filed February 10, 1994. The appealed claims

have an effective filing date of October 31, 1997, since neither the particular identification method for compounds nor a diabetes treatment method is disclosed in 08/194468. The state of the prior art at the time the invention was made is appropriately determined as of no earlier than October 1997. The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, published 1999, provides at least an indication of the state of the art with respect to diabetes treatment at or about the time the invention was made (The Sixteenth Edition of the Merck Manual of Diagnosis and Therapy was published in 1992.). The Merck Manual does not indicate that inhibition or disruption of CREB-CBP binding is a known mechanism of action for any recognized diabetes treatment, including insulin, the sulfonylureas, and various hyperglycemic drugs. Since the state of the art at the time the invention was made provides no information that would aid one of skill in the art in knowing how to treat diabetes using a compound that inhibits or disrupts CREB-CBP binding, in the absence of evidence to the contrary, one wishing to practice the claimed invention must rely solely on Applicant's disclosure for guidance.

The specification of the instant application mentions diabetes treatment in six places, as cited above.

The specification provides Examples I-V, all of which are *in vitro* studies that concern the properties of CBP and the nature of its interactions with other proteins. Neither the specification nor the state of the art at the time the invention was made provides a basis for correlating results obtained in these *in vitro* studies with any beneficial effect to be had by practicing a method of treating diabetes by administering a

compound, not further described, that inhibits binding of cyclic AMP response element binding protein, CREB, to CREB binding protein, CBP, or that disrupts a complex comprising CREB and CBP. Applicant's disclosure provides, at best, predicted results rather than results actually obtained and does not alone provide sufficient guidance for one of skill in the art to practice the invention as claimed without undue experimentation.

Applicant has previously argued, in Paper No. 15, filed July 15, 2002, that the Examiner has "required Applicant to demonstrate that the inventive mechanism of action was accepted in the art prior to the filing of the application"; has asserted that the fact that Applicant's [invention's] mechanism of action was not disclosed in the Merck Manual lacks relevance to the question of enablement; and has cited post filing publications (Mayr et al. and Herzig et al., of record) by the inventor "describing the inventive methods and asserting its use in treating diabetes mellitus." Applicant has stated that the Examiner "appears to accept that the screening method for identifying inhibiting compounds described in the application is enabled," and that the Examiner "continues to insist" that clinical data are required to demonstrate that a compound exists that has both the binding-inhibitory effect required and is effective to treat a human with diabetes. Applicant has argued that there is no evidence that the Merck Manual is a reliable source for the latest in diabetes treatment methods and mechanisms of action and that it does not provide mention of new methods of treatment as represented in newly issued patents, of which Applicant cites ten by patent number (now of record, PTO 1449 filed November 27, 2002). Applicant has argued that the Mayr et al. reference states that CREB functions in glucose homeostasis and that the

conclusions stated in Mayr et al. are consistent with Applicant's disclosure teaching involvement of CREB-CBP complex in diabetes. Applicant has argued that the Herzig et al. article reports that CREB controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator PGC-1, and uses normal and diabetic animals to show that reduced CREB activity causes fasting hyperglycemia *in vivo*, which Herzig et al. states "is correlated with Type II diabetes." Applicant points to the specification as providing guidance in formulation and dosage. Applicant has argued that there is no *per se* requirement for human clinical data to enable a method of therapy. Applicant has alleged that the Examiner failed to consider the Mayr et al. and the Herzig et al. references as evidence because they were published after the filing date of the application and use methods to obtain results that go beyond those instantly disclosed and has urged that they are relied upon to prove the truth of statements in Applicant's disclosure rather than to supplement the disclosure itself.

Applicant's arguments have been considered but not found to be persuasive. The Examiner has not required Applicant to demonstrate that the inventive mechanism of action was accepted in the prior art, and has not required Applicant to provide clinical data; rather, the citation of material from the Merck Manual was done purely to help establish the state of the art at, or about, the time the invention was made. Further, the Examiner has made no mention of the presence or absence of clinical data, but rather has noted that Applicant has provided no basis for correlation of the *in vitro* examples provided in the specification with an *in vivo* treatment for diabetes using a compound that is specified only by a method for identifying it. It is agreed that a method to identify

compounds which disrupt complex comprising CREB and CBP is enabled; see claims 1-6 of US Patent No. 6,063,583. With respect to the patents cited by Applicant to support the assertion that patents have been issued whose mechanism of action is not disclosed in the Merck Manual, the assertion is not evaluated here since Applicant has provided no detailed discussion of the mechanisms of action of treatment represented in each of the patents and no discussion of how such information is relevant to the rejection claims. It is noted that the prosecution of a particular patent application generally has no bearing on the prosecution of any other application. With respect to the citation of the Mayr et al. and the Herzig et al. references, a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling and cannot be used to show what was known at the time of filing. With respect to Applicant's assertion that the Mayr et al. and Herzig et al. are relied upon to prove the truth of statements in Applicant's disclosure rather than to supplement the disclosure itself, even if Applicant relies upon Mayr et al. to show that CREB functions in glucose homeostasis and that the conclusions stated in Mayr et al. are consistent with Applicant's disclosure teaching involvement of CREB-CBP complex in diabetes, the Mayr et al. reference does not teach that a compound identified by Applicant's method has a beneficial effect when used to treat diabetes. Even if Applicant relies upon Herzig et al. to show that CREB controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator PGC-1, and uses normal and diabetic animals to show that reduced CREB activity causes fasting hyperglycemia *in vivo*, Herzig et al. does not teach that a compound identified by Applicant's method has a

beneficial effect when used to treat diabetes. Further, Herzig et al., published in September 2001, supports the unpredictability and the amount of experimentation remaining in the field nearly four years after Applicant's effective filing date: "The effect of A-CREB on liver gene expression suggests that CREB **may** constitute an ideal target for therapeutic intervention. Although use of a dominant negative inhibitor such as A-CREB may not be feasible in this regard, small molecules that block CREB phosphorylation or disrupt recruitment of the CREB coactivator CBP (CREB binding protein) **may** prove effective. Such compounds **may** be particularly beneficial as adjunctive therapy in lowering fasting blood glucose levels in type II diabetes." (See Herzig et al., page 182, second column, second full paragraph; emphasis added.)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
June 12, 2003